The impact of Pavlovian cues on pain avoidance: a behavioral study

Nathalie Claes[1, 2], Geert Crombez[2, 3], Mathijs Franssen[1], Johan W.S. Vlaeyen[1, 4]

[1]Research Group Health Psychology, Faculty of Psychology and Educational Sciences, University of Leuven, Belgium

[2]Department of Experimental-Clinical and Health Psychology, Faculty of Psychology and Educational Sciences, Ghent University, Belgium

[3]Centre for Pain Research, University of Bath, Bath, United Kingdom

[4]Department of Clinical Psychological Science, Maastricht University, The Netherlands

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Correspondence concerning this article should be addressed to Nathalie Claes, Department of Psychology, University of Leuven, Tiensestraat 102, box 3726, 3000 Leuven, Belgium. E-mail: Nathalie.claes@kuleuven.be, T: +32 (0)16 32 58 85, F: +32 (0)16 32 61 44.

URL: https://ppw.kuleuven.be/home/english/research/ogp/nathalie

Abstract

This experiment investigated whether Pavlovian cues predicting pain would increase pain-related avoidance behavior. For this purpose, forty-two healthy participants first completed an instrumental acquisition phase, performing three different movements with a pneumatic robot arm. One movement was associated with 80% chance of painful stimulation and required the least effort to perform, another movement was associated with 50% chance and required intermediate effort to perform, and yet another movement was associated with no chance of stimulation, but required the most effort to perform. Next, participants could choose which of these movements they performed. Subsequently, participants learned to associate three different Pavlovian cues with the painful outcome, a reward consisting of two lottery tickets, or neither of these outcomes. In the test phase, comprised of free and restricted parts, these Pavlovian cues were integrated in the movement task, such that the movements were carried out in the presence of one of the cues. Contrary to our hypothesis, presenting a pain cue resulted in a relative decrease in avoidance behavior compared to the presentation of no cue, a neutral cue or a reward cue, although the safe option was still selected most often, regardless of the cues present. Possible explanations for our findings are outlined in the discussion.

Keywords: Fear, pain, classical conditioning, instrumental learning, avoidance

1. Introduction

Selecting an appropriate response in the face of a changing environment is a fundamental characteristic of human behavior (Cohen-Hatton, Haddon, George, & Honey, 2013; Emmons, 1986). More specifically, being capable of identifying an event as threatening, emitting a fearful response, and consequently avoiding it is considered adaptive, and in some cases could mean the difference between life or death. However, these avoidant responses may become maladaptive when used excessively, or when emitted in the absence of real threat. Maladaptive avoidance is considered a central characteristic in many mental disorders (Barlow, 2002; Krypotos, Effting, Kindt, & Beckers, 2015). Similarly, contemporary cognitive-behavioral models of chronic pain posit that misconceptions about painful experiences may give rise to fear and avoidance, which may lead to disuse and disability, severely affecting patients' lives (Vlaeyen & Linton, 2000; 2012). For example, a patient experiencing chronic pain may refrain from valued activities out of fear that doing so will exacerbate the pain that is already present. In the past, theories of avoidance learning often proposed that fear—or more specifically, the reduction thereof—is primarily responsible for the maintenance of avoidance behavior (e.g., Mowrer, 1951). Often, avoidance was described as the behavioral component of fear—next to a verbal (e.g., self-reports) and a physiological component (e.g., skin conductance) of fear—and was considered to covary with fear (Lang, 1968). However, the necessity of fear (reduction) for avoidance behavior has been challenged, and it is posited that fear and avoidance might act or be affected independently (Beckers, Krypotos, Boddez, Effting, & Kindt, 2013; Krypotos et al., 2015; Rachman & Hogdson, 1974; Volders, Boddez, De Peuter, Meulders, & Vlaeyen, 2015). In the field of experimental pain research, Claes and colleagues (Claes, Crombez, & Vlaeyen, 2015; Claes, Karos, Meulders, Crombez, & Vlaeyen, 2014) have demonstrated that a concurrent reward did not alter pain-related fear but decreased avoidant behavior.

Adaptation to changing environments is also facilitated by cues that signal particular outcomes, or the absence thereof (Brackbill & Overmier, 1979; Doya, 2008). As such, cues can guide *goal-directed* behavior, but not necessarily in an adaptive way (Holmes, Marchand, & Coutureau, 2010). This modulation of instrumental responding by Pavlovian cues is termed Pavlovian-to-Instrumental transfer (PIT; e.g., Estes, 1943). Two types of PIT can be differentiated. General PIT occurs when Pavlovian cues increase the rate of instrumental responding, even though they have never been associated with a similar outcome as the instrumental response. Pavlovian cues can also selectively increase the rate of responding for the instrumental response associated with that particular outcome, which is termed selective PIT. PIT has mainly been studied considering appetitive responding in non-human animals, and only recently in humans (Cohen-Hatton et al., 2013; Dickinson & Balleine, 1994; Holmes et al., 2010; Talmi, Seymour, Dayan, & Dolan, 2008). In contrast, the modulation of instrumental avoidance by Pavlovian stimuli has received much less attention. Only recently it was demonstrated that when a cue signaling a specific aversive outcome was presented, instrumental (avoidance) responding was selectively increased (Lewis, Niznikiewicz, Delamater, & Delgado, 2013). These authors also observed a general PIT effect, with cues predicting a dissimilar yet aversive outcome increasing overall instrumental behavior. Given the potential detrimental consequences of pain avoidance, it might be fruitful to further explore the impact of Pavlovian cues on avoidance behavior. In the field of chronic pain research, there have been calls to further explore the impact of context and motivation on pain-related behavior to improve our understanding of the mechanisms underlying the development, maintenance, and exacerbation of chronic pain problems (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012; Eccleston & Crombez, 1999; Vlaeyen, Crombez, & Linton, 2009). One of our previous studies demonstrated that a cue predicting pain increased pain-related fear and avoidance tendencies, whereas cues predicting reward decreased these tendencies (Claes, Vlaeyen, & Crombez, 2016). In the current experiment, we therefore focus specifically on the impact of Pavlovian cues on the avoidance of painful movements. Participants learned to associate different Pavlovian cues with either a painful electrocutaneous stimulus, lottery tickets—or neither of these outcomes. These Pavlovian cues were then integrated in an instrumental movement task, in which participants could choose to perform movements that were either followed by a painful stimulus in 80% of the trials, in 50% of the trials, or never followed by a painful stimulus (safe movement). We expected that the Pavlovian cue predicting a similar, aversive outcome would increase avoidance behavior. That is, in the presence of a pain cue, the safe movement was expected to be selected more often, as compared to a neutral Pavlovian cue and a Pavlovian cue predicting an appetitive outcome. Similarly, we expected that response latencies would be increased when a Pavlovian cue was presented compared to when a cue was absent, and that the presentation of a Pavlovian cue predicting pain would further increase response latency as compared to a neutral or reward Pavlovian cue. Furthermore, in line with Puca, Rinkenauer, and Breidenstein (2006), we expected that when avoidance was no longer possible, participants would initially put more effort into avoiding the painful movement when the presented Pavlovian cue predicted pain, as compared to when it predicted reward, nothing or was absent.

2. Methods

2.1 Participants

Forty-six healthy Dutch-speaking volunteers—11 males—aged between 18 and 36 years (Mean age: 23.28 ± 3.84 years) participated in the study. Volunteers were recruited via the online recruitment system of the Faculty of Psychology and Educational Sciences of the KU Leuven and flyers distributed on campus and social media. All participants received a financial remuneration of € 15. Exclusion criteria based on self-report were: cardiovascular diseases, lung diseases, neurological diseases (e.g., epilepsy), other serious medical conditions, not being able to freely move the arms, hands and/or shoulders, chronic pain, acute pain or discomfort located at the wrist/hand/shoulder or related body regions, being asked to avoid stressful situations by a general practitioner, presence of electronic medical devices (e.g., pace-maker), pregnancy, use of recreational drugs or medication affecting the intestines or central nervous system, recovering from severe trauma or surgery, or hearing problems and impaired vision that is not corrected (including color blindness). Some task-related exclusion criteria were formulated as well: unsuccessful learning of the contingencies in either of the acquisition phases—defined as incorrectly answering the contingency check on four subsequent instances —or indicating that both pain-avoidance and reward-seeking were unimportant. The Social and Societal Ethics Committee (SMEC) of the KU

Leuven (Belgium) approved the study protocol (reg. no. G- 2014 12 117). All participants provided their written informed consent.

One participant indicated that both pain-avoidance and earning tickets were unimportant. For 3 participants, there was a technical error, resulting in incomplete data. These 4 participants were excluded from further analyses. The final sample size was 42—9 male—with a mean age of 22.95 ± 3.47 years.

2.2 Apparatus and Software

The experiment was compiled in Microsoft ® Visual Studio, mainly programmed in C/C++, using OpenGL and HM API; and run on an Windows 7 Professional (64 bit) computer (Dell OptiPlex 9020, Dell, Round Rock, TX) with 2 GB Random-access memory (RAM) with an Intel Core i7-4770 processor (Intel, Santa Clara, CA) at 3.4 GHz and an AMD Radeon™ R7 250 graphics card (Advanced Micro Devices, Sunnyvale, CA) with 4 GB of video RAM. The experiment was displayed on a 46-inch Philips TV, model 36PFL3208K/12. Participants could select their answers with a Targus numerical keyboard.

2.3 Stimuli

Painful, electrocutaneous stimuli of 2ms in duration (square waveform) delivered by an Isolated Bipolar Current Stimulator (DS7A; Digitimer ltd, Welwyn Garden City, England) served as the pain outcome. Participants received these stimuli via two surface electrodes (V91-01, Ø 8 mm, Coulbourn Instruments, Whitehall, PA, USA) filled with K-Y gel (Johnson & Johnson, New Brunswick, NJ) attached to the upper right arm at the height of the elbow. The level of stimulus intensity was determined during an individual calibration procedure (see Preparation phase). Lottery tickets—represented by a yellow star on screen—served as the reward outcome. One lottery ticket corresponded with one chance to win a self-selected lottery prize worth approximately € 100 (Claes, Crombez, & Vlaeyen, 2015).

2.4. Experimental tasks

The procedure used followed a structure similar to studies on Pavlovian-to-Instrumental transfer (Holmes et al., 2010; Lewis et al., 2013).

In a first, *experimental movement task,* participants executed arm extensions with their right arm using a pneumatic robot arm called the Haptic Master (MOOG Inc., East Aurora, New York, USA), which is a three-degrees of freedom, force-controlled haptic interface. The experimental movement environment allowed movement along the horizontal movement plane (X- & Y-axis), whereas movement along the z-axis was restricted (see Fig. 1). The starting point—a red cube of 3.5 by 3.5 cm—was fixed at the bottom left of the movement environment. Similarly, the end point— a red gate of 11.5 cm—was fixed at the top left of the movement environment. In the middle of the movement environment, three red gates of equal width and height represented three different movement paths (left, middle, right). The three movement paths corresponded with 80% chance of painful stimulation, 50% chance of receiving a painful stimulus, and safety, respectively (similar to Meulders, Franssen, Fonteyne, & Vlaeyen, 2016). Additionally, the Haptic Master exerted 5 N force, making performing movements deviating from the left path more difficult, thus creating a trade-off between effort and pain.

In the Pavlovian learning task, three different neutral cues served as conditioned stimuli (CSs). The cues were a Fire flower, a Blooper, and a Super Mushroom icon (Super Mario Bros, Nintendo ®, Kyoto, Japan). One cue was associated with the pain outcome (Pain CS); another cue was associated with the reward outcome (reward CS); whereas the last cue was associated with neither (Neutral CS). Cue-outcome associations were counterbalanced between participants. In the test phase, CSs were integrated in the instrumental movement task.

- INSERT FIGURE 1 ABOUT HERE -

2.5 Measures

2.5.1 Self-reported measures

2.5.1.1 Pain rating electrocutaneous stimulus. During calibration, participants rated the "pain intensity" of the electrocutaneous stimulus on an 11-point Likert scale ranging from 0 (no pain) to 10 (worst pain imaginable), and on a verbal rating scale reading "Light – medium – serious – enormous". Pain unpleasantness and pain tolerance were equally assessed on an 11-point Likert scale ranging from 0 (not at all) to 10 (very much).

2.5.1.2 Rating lottery prize and lottery tickets. Upon selection of a lottery prize, participants assessed the how difficult it was to select a prize, their interest in winning the prize, the value of the prize, how much effort they were willing to exert to win the prize on an 11-point Likert scale ranging from 0 (not at all) to 10 (very much). Participants also estimated their chance of winning the lottery (in percentages). Additionally, the value and pleasantness of the tickets were rated on an 11-point Likert scale ranging from 0 (not at all) to 10 (very much). The value of the tickets was also assessed using a verbal rating scale with the following labels: "light – medium – serious – enormous".

2.5.1.3 Goal measures. Before the experimental task started, participants reported the goals they held for the experiment. First, they could sum up their specific goals for this experiment in response to an open question. Next, they ranked each of the following goals according to their importance from 1 to 4: "successfully completing the experiment", "avoiding the painful stimulus", "learn the associations as well as possible", and "earn as many tickets as possible". Participants also rated each goal's importance on a scale from 0 (not important at all) to 10 (very important). Additionally, participants were asked to indicate which of the following goals was most important: "reward-seeking", "pain-avoidance", "both equally important", or "both equally unimportant".

2.5.1.4 Pain-related fear. After successfully learning the contingencies in the instrumental movement task, participants indicated how afraid they were of a specific movement path (lit-up on screen) on an 11-point Likert scale ranging from 0 (not at all) to 10 (very afraid). Similarly, after having successfully learned the cue-outcome associations in the Pavlovian learning procedure, participants indicated how afraid they were of each of the Pavlovian cues using the same Likert scale.

2.5.1.5 Questionnaires. Upon completion of the experiment, participants filled in sociodemographic information and the Dutch version of the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scales (Franken, Muris, & Rassin, 2005) online. The BIS is thought to reflect sensitivity to punishment and avoidance motivation, whereas BAS reflects reward sensitivity/approach motivation. The BAS scale is divided into three subscales (a drive scale, a fun seeking scale, and a reward responsiveness scale), as it is believed that they focus on different aspects of reward sensitivity. These measures were collected for descriptive purposes only.

2.5.2 Behavioral measures

2.5.2.1 Maximal movement distance. For each movement trial, the total trajectory of the movement was mapped from movement-onset until completion of the movement. Maximal movement distance refers to the point on this trajectory furthest away from the outer left wall of the movement field on the x-axis (corresponding with a value of -0.18). Maximum movement distance ranges from -0.18 to 0.18 (see Fig. 1), with higher values indicating more avoidant behavior.

2.5.2.2 Movement choice. On each movement trial, we recorded which movement path was chosen by the participant. Moving along the left path, associated with 80% of painful stimulation was coded as a '1', moving along the middle path associated with 50% of painful stimulation was coded as '2', and the right, non-painful path, as '3'. Movement choice is a measure of avoidance behavior, with a higher number indicating more avoidant behavior.

2.5.2.3 Response latency. Time of movement-onset was recorded on every movement trial, and operationalized as the time in seconds between the start signal (auditory) and leaving the start region (red cube; 10% of the total y-axis area).

2.5.2.4 Response duration. Similarly, time of movement completion was recorded, and defined as the time in seconds between leaving the start region and reaching the end point (red gate), as announced by an auditory stimulus.

2.5.2.5 Force. During instructed test trials with fixed trajectories, the force in Newton participants exert in order to avoid performing movements along the left path was recorded.

2.6 Procedure

The study was conducted in a sound-attenuated experimental room located at the Faculty of Psychology and Educational Sciences, KU Leuven (Belgium). An experimental session lasted about 90 min.

2.6.1 Preparation phase

Upon arrival in the laboratory, participants received oral and written information on the purpose and course of the study, and were provided with the opportunity to ask for clarification before giving informed consent. The experimenter (female; A.D.K; N.C.) informed the participants that during the experiment, they would be exposed to painful electrocutaneous stimuli, but that the level of stimulus intensity would be individually determined. Participants were given stimuli of increasing intensity, and were asked to rate pain intensity, pain unpleasantness and pain tolerance after every stimulation. There was at least 20 s between stimulations. Participants could indicate when they no longer wished to increase stimulus intensity but they were asked to select a stimulus that was painful and required some effort to tolerate, which corresponds roughly with a stimulus rated at least 8 on pain intensity and a 6 on the pain tolerance. The experimenter asked each participant whether s/he agreed to repeatedly receive stimuli of the maximally selected intensity before continuing the experiment. Subsequently, the experimenter explained that lottery tickets could be earned during the experiment, with which they could win a prize of their choice worth approximately € 100. The experimenter requested participants to select one prize out of a list of 36 possible prizes and to fill in the questions related to their prize. Next, the experimenter stated that the more tickets participants earned, the more chance they had of winning their prize. Next, participants assessed ticket value and ticket pleasantness. Lastly, the experimenter asked the participants to complete the goal-related questions.

2.6.2 Practice phase

Participants were asked to practice the use of the numeric keyboard to answer the questions and to perform movements with the Haptic Master before advancing to the first experimental task. First, the experimenter informed the participant that during the experimental task, the participant would be requested to answer questions using the numeric keyboard. To get acquainted with the use of the keyboard, the experimenter showed the different question types on screen as they would appear during the task, and instructed the participant to select an answer option (e.g., “select the middle gate”; “give a score of 10”). Participants could practice until they felt confident in using the numeric keyboard. Next, the experimenter explained that participants would make arm extension movements with the Haptic Master, and now had the opportunity to practice these movements, without receiving electrocutaneous stimuli or lottery tickets. The experimenter demonstrated a movement through each gate, and consequently asked the participant to move through each gate at least twice. Again, participants were asked to practice until they felt confident in handling the Haptic Master and to respond to the auditory start signal administrated via headphones by moving through one of the gates of their choice and reaching the end gate. Successful completion of a movement was announced using an auditory signal. Upon movement completion, the Haptic Master automatically moved back to the start position. A new trial started after 100 ms. Some examples of actual performed movements are presented in Figure 2.

-INSERT FIGURE 2 ABOUT HERE-

2.6.3 Instrumental acquisition phase

In this phase, participants were instructed to perform movements through one of the three gates as soon as they heard the start signal and were informed that movements would now be associated with either (a) an 80% chance of receiving a painful stimulus, (b) a 50% chance of receiving a painful stimulus, or (c) no painful stimulation, and it was up to them to learn which movement path was associated with each outcome.

It was also mentioned that some movements would require more effort than others to perform. No lottery tickets could be earned during this phase. Participants could choose the order in which they performed the movements but completed 12 arm extensions per movement path (36 movements in total). For each participant, a movement straight ahead (left gate) was associated with an 80% chance of painful stimulation, but it was also the easiest to perform; the middle gate was associated with a 50% chance of painful stimulation and was associated with some resistant force; and the right gate was never followed by painful stimulation but was at the same time the hardest to perform. Painful stimuli were administrated upon completion of the movement. Upon completion of this first block, a contingency check was administered. Participants were asked to indicate which movement path was associated with 80%, 50%, and no painful stimulation by selecting the corresponding gate using the numeric keyboard. If participants were unsuccessful in learning the contingencies, they completed another block of 36 movements and were again presented with the contingency check questions. Participants could complete up to three additional blocks. If the last contingency check was answered incorrectly, the experiment ended for these participants. If participants answered the questions correctly, they rated the level of pain-related fear for each of the movement paths. The course of a trial was similar as in the practice phase, with the difference that total trial timing (auditory start signal to start new trial) was set at 7500 ms. Intertrial interval time varied in duration dependent on the movement duration.

2.6.4 Baseline free operant phase

When the movement-pain outcome contingencies were successfully learned, participants were instructed to again perform arm extensions, but that they now could choose which movement they made. As such, they no longer were requested to move through each gate. The instructions made clear that the contingencies from the previous phase still held. Participants performed 12 movements in total. We a priori determined a reinforcement plan for each of the movement paths that corresponded with 80%, 50%, and no reinforcement, respectively. Participants' response latency, response duration, total movement distance, and movement choice were registered for each trial.

2.6.5 Pavlovian acquisition phase

Next, participants were asked to complete a second learning task, in which they would be presented with different cues (CSs), which either predicted the painful stimulus, the reward outcome, or neither outcome. The aim of the task was to learn the cue-outcome contingencies. A trial started with a 100-ms presentation of a fixation cross, followed by the presentation of the CS at the top of the screen, accompanied by the outcome after 100 ms. Participants were presented with 1 block of 4 presentations of each CS. The pain CS was accompanied by the pain outcome on 75% of the trials, and the reward CS by the reward outcome on 75% of the trials; the neutral CS was never reinforced. Cue-outcome contingencies were counterbalanced between participants. As in the instrumental acquisition phase, a contingency check was administered. Participants were asked to indicate what each specific cue predicted using the numeric keyboard: (a) painful stimulation, (b) lottery tickets, and (c) nothing. If participants answered the questions incorrectly, participants were presented with up to 3 additional blocks, after which the experiment was stopped. If participants successfully learned the cue-outcome contingencies, they rated their pain-related fear for each of the cues.

2.6.6 Free Pavlovian-Instrumental test phase

Next, participants were informed that in the next phase, the cues would be integrated in the movement task. Instructions stated that participants again were asked to perform arm extensions of their choice, as soon as the start signal sounded. Furthermore, instructions stressed that the *movement - pain outcome* associations still held. That is, the three movement paths were associated with 80%, 50%, and 0% chance of painful stimulation, respectively. In total, participants were presented with 4 blocks of 3 pain CSs, 3 reward CSs, 3 neutral CSs, and 3 no-CS trials (48 trials in total). We a priori determined a pseudo-random reinforcement plan, as the first selection of an 80% or a 50% chance of pain pathway always resulted in the administration of the painful stimulation, whereas overall, the typical movement-outcome contingencies were in place for each CS type. For example, if a participant selected the left pathway on every trial where a reward cue was presented, 80% of the movements were followed by a painful stimulus. We registered response latency, response duration, total movement distance, and movement choice for each trial.

2.6.7 Restricted Pavlovian-Instrumental test phase

Immediately following the free Pavlovian-Instrumental test phase, the restricted test phase ensued. An invisible wall was placed between the left and middle gate in the movement environment. Hence, participants could only perform the left movement path. At the same time, we measured the exerted force (effort) to avoid when avoidance was no longer possible. Participants completed 12 trials in total, 3 blocks of 1 trial per CS type (Pain CS/reward CS/neutral CS/no CS). All movements were followed by a painful stimulus. No lottery tickets were provided.

2.6.8 Debriefing

Upon completion of the experimental task, the experimenter requested participants to fill in the questionnaires online. The course of the lottery was explained, as was the aim of the experiment. Participants could leave their contact information so that they could be contacted if they won the lottery and if they wished to be informed about the results of the study. The computer randomly selected one of the participants as the winner of the lottery.

3. Results

3.1 Data-analytic strategy

To examine the effect of CS type on the maximum movement distance, response latency, and movement duration, we conducted separate 4 × 4 (CS type [None/Pain/Reward/Neutral] × block [1/2/3/4]) repeated measures analyses of variance (ANOVA) during the free test phase. For the variable movement choice, we conducted a Chi Square Test to examine the overall effect of CS type. For force during the restricted test phase, a repeated measures ANOVA with CS type (None/Pain /Reward/Neutral) and block (1/2/3) as within-subject factors was calculated. Follow-up contrasts are reported when appropriate. All analyses were conducted using SPSS 22.0 (SPSS Inc., Chicago, IL), and Microsoft® Office Excel 2010. Alpha levels were set at .05. When Mauchly's test of sphericity was violated, Greenhouse Geisser corrections are reported. Where appropriate, generalized eta squared (η_G^2) is reported as a measure of effect size (Bakeman, 2005; Lakens, 2013; Olejnik & Algina, 2003).

3.2 Descriptive statistics

3.2.1 Pain stimulus descriptives

The average tolerable stimulus intensity was 26 mA (± 1.35 mA). On average, participants indicated the selected stimulus was painful, and gave a score of 8.40 (± 0.63) on the painfulness scale. The average scores for unpleasantness and tolerability of the stimulus were 8.26 (± 1.01) and 7.93 (± 0.97), respectively. Most participants (52.4%) chose to enter the lottery to win an additional € 100 or gift vouchers for different companies (23.9%). The value of the selected prize was rated 7.05 (± 2.65). Participants scored the difficulty to select a prize 4.52 (± 2.83), and the interest in winning the lottery prize 7.86 (± 2.4). The amount of effort they were willing to exert was rated 7.71 (± 1.83). Participants indicated that the lottery tickets were valuable, and on average scored ticket value 7.21 (± 2.35). Mean pleasantness of the ticket was 8.24 (± 1.95).

3.2.2 Goal measures

The importance of avoiding pain during the experiment was rated on average 6.31 (± 2.34). The importance of earning lottery tickets during the experiment was rated 6.81 (± 2.66). These ratings did not differ significantly, $t(41) = -1.174$, $p = .247$. Sixteen participants indicated that both goals were equally important; 17 indicated earning lottery tickets was the most important goal; 6 preferred to avoid pain over earning lottery tickets.

3.2.3 Questionnaires

Participants had an average score of 23.55 (± 3.81) on the BIS scale, 11.86 (± 2.08) on the BAS drive scale, 11.07 (± 2.04) on the BAS fun seeking scale, and 17.48 (± 2.03) on the BAS reward responsiveness scale.

These scores are similar to average scores obtained in a sample of Dutch-speaking students (Smits & Boeck, 2006) and a general population (Jorm et al., 1998).

3.2.4 Baseline behavior

The maximum movement distance ranged from -0.123 to .144, with a mean maximum movement distance of .062 (± 0.069). Participants most often chose the safe path (66%), whereas the paths corresponding with 80% and 50% chance of pain were only selected in 17% of the trials each. The mean response latency was 418 (± 141) ms. The mean movement duration was 2580 (± 825) ms. Baseline behavior did not differ significantly from test trials where no CS was presented, *p*s > .084.

3.3 Manipulation check

The majority of participants (30, 71.4 %) successfully learned the contingencies in the instrumental acquisition phase after 1 block; 8 participants needed one additional block; 4 participants needed 2 additional blocks. Similarly, for the Pavlovian acquisition phase, the majority of participants (34, 80.9 %) learned the contingencies after completing 1 block; 5 participants needed 1 additional block, 2 participants needed 2 additional blocks, and 1 participant needed 3 additional blocks.

For pain-related fear, ANOVA analysis revealed a main effect of pathway, $F(2, 817) = 151.11$, $p < .001$. Follow up comparisons revealed that in the instrumental acquisition phase, participants reported being more afraid to perform a movement associated with the left—most painful—path (6.43 ± 2.39) than a movement associated with the middle path (5.36 ± 1.82), $t(41) = 4.26$, $p < .001$. In turn, they reported being more afraid of the middle path movement than the movement associated with the right—safe—path (0.57 ± 1.25), $t(41) = 13.48$, $p < .001$. In the Pavlovian phase, analysis revealed a main effect of cue, $F(2, 1213.635) = 361.36$, $p < .001$. Follow-up analyses showed that participants reported being more afraid of the pain cue (7.24 ± 1.9) than of the neutral cue (0.62 ± 1.08), $t(41) = 19.83$, $p < .001$. There was no difference in fear ratings for the neutral cue and the reward cue (0.69 ± 1.3), $t(41) < 1$, $p = .607$.

Interestingly, participants were more afraid of the pain cue than the movement associated with the left path, $t(41) = -2.52$, $p = .016$.

3.4 Behavioral measures

3.4.1 Maximum movement distance

There was a significant main effect of block, as well as CS type, $F(3, 123) = 2.98$, $p = .047$, $\eta_G^2 = .0106$ and $F(3,123) = 7.9$, $p = .001$, $\eta_G^2 = .0639$, respectively. There was however no Block × CS type interaction, $F < 1$ (see Fig. 3). Upon closer inspection, it seems that at block 1, there was no difference in maximum movement distance when there was no cue presented compared to the presentation of a cue, *p*s > .105. However, participants seemed to avoid less when presented with a pain cue compared to the neutral cue and the reward cue, $t(41) = -3.816$, $p < .001$ and $t(41) = -4.221$, $p < .001$, respectively. These differences were still present at block 4, pain cue vs. neutral cue: $t(41) = -2.747$, $p = .009$; pain cue vs. reward cue: $t(41) = -2.471$, $p = .018$.

- INSERT FIGURE 3 ABOUT HERE -

3.4.2 Movement choice

The analysis revealed a significant association between CS type presented and the movement choice, $\chi^2(6) = 145.85$, $p < .001$. There was a larger than expected number of times participants chose the paths associated with 80% and 50% contingency when presented with a pain cue. It should however be noted that overall, participants chose the safe path on at least 42% of the trials when a pain cue was presented (as compared to 59-69% when presented with other cues).

3.4.3 Response latency

The analyses yielded a main effect of block, $F(3, 123) = 14.81$, $p < .001$, $\eta_G^2 = .1117$, and a main effect of CS type, $F(3,123) = 3.2$, $p = .035$, $\eta_G^2 = .0111$ (see Table 2). The CS type × block interaction was not significant, $F(9,369) = 2.06$, $p = .105$, $\eta_G^2 = .0162$. Planned contrasts revealed that participants initiated the movement faster when there was no cue presented compared to when they were presented with a pain cue, $F(1,41) = 6.44$, $p = .015$. There was no difference in response latency between the pain cue and the reward cue, nor between the reward cue and the neutral cue, *p*s > .129.

3.4.4 Response duration

The results showed that participants became gradually faster over time, main effect of block, $F(3, 123) = 10.336$, $p < .001$, $\eta_G^2 = .0528$. There was however no effect of CS type, $F(3, 123) = 1.41$, $p = .249$, $\eta_G^2 = .0062$, nor an interaction between CS type and block, $F(9, 369) = 1.3$, $p = .272$, $\eta_G^2 = .0118$ (see Table 1).

- INSERT TABLE 1 ABOUT HERE -

3.4.5 Force

Force exerted during the restricted test phase: the results only yielded a significant main effect of block, $F(2, 82) = 51.91$, $p < .001$, $\eta_G^2 = 0.182$, indicating that participants exerted less force over time. Both the main effect of CS type and the interaction were not significant, *p*s > .974.

4. Discussion

The current study investigated the impact of Pavlovian cues on pain-motivated avoidance behavior. More specifically, we incorporated Pavlovian cues predicting either pain, reward, or neither in an instrumental avoidance task to uncover whether cues predicting pain would increase pain avoidance. Contrary to our previous experiment (Claes et al., 2016) and our hypothesis, this study demonstrated that a Pavlovian cue predicting a painful outcome resulted in a relative decrease in avoidance behavior compared to the presentation of no cue or a neutral cue, as was evident in the maximal movement distance, as well as the more frequent selection of movements associated with 80% and 50% chance of stimulation. However, it should be noted that the safe movement (=complete avoidance) was still selected in 42% of the trials. These findings are surprising. First, participants were explicitly instructed to move as they pleased and to ignore the Pavlovian cues. Second, they go against the Pavlovian-to-Instrumental transfer effects described in the literature (Holmes et al., 2010; Nadler, Delgado, & Delamater, 2011; Van Meurs, Wiggert, Wicker, &

Lissek, 2014). Although these results may seem contra-intuitive, there may be a viable explanation. In the remainder of the paper, we will present possible reasons for our unexpected findings.

First, it may well be that the results are driven by a particular subgroup of individuals. One characteristic especially relevant in studying PIT is motivation. Motivational dual-process theoretical accounts (Balleine & Ostlund, 2007; Mowrer, 1947, 1951) state that Pavlovian cues may interfere with goal-directed action (De Wit & Dickinson, 2009; Huys et al., 2011). In our experiment, participants were firstly instructed to perform the movements as quickly as possible. As is often the case in experimental research, participants' main goal was to complete the task as is required. The action best matching this goal is to perform movements straight ahead, which were also the movements associated with the highest chance of pain. Moreover, we also asked participants which goal they deemed most important during the experiment, either pain-avoidance, reward-seeking, or both equally important. Based on these goals, the same action may be considered in light of their goal: a painful movement that is also the fastest and the less effortful matches the goal of the reward-seeking individual who wishes to complete the task and earn 'points', whereas it conflicts with the pain-avoidance goal. To explore the effects of general motivation, we examined the patterns emerging in our different groups based on their prioritized goal. The patterns were as follows: pain-avoiders (N=9) showed a significant general increase in avoidance behavior (selecting the safe but effortful movement) in the presence of a cue, compared to when a cue was absent. This behavior was more pronounced when the cue signaled pain. Reward-seekers (N=17) and participants who found both goals equally important (N=16) showed a significant decrease in avoidance behavior (selecting painful but less effortful movement) when the Pavlovian cue signaled pain and an increase in avoidance behavior when the cue signaled reward or neither pain nor reward compared to the absence of a Pavlovian stimulus. This difference between individuals seems to suggest that Pavlovian cues predicting pain indeed contribute to increased avoidance, but only if the individual is primarily motivated to avoid pain. In other words: the expected pattern of responding was found in the pain-avoiders group only. Future research should incorporate a priori motivation when studying the impact of Pavlovian cues on motivated (avoidance) behavior, either by recruiting according to motivation, or by manipulation of motivation, possibly via verbal instructions, to increase power. In a context of chronic pain, the latter might be especially interesting, because it might provide insights as to how clinicians' instructions to patients may potentially impact patients' choices. It should be noted that in the pain-avoiders group, the increase in avoidance behavior was non-specific, since both presenting a neutral and a reward cue increased avoidant responding as well. This differentiation between presence and absence of a Pavlovian cue was also evident in the response latency data for the group as a whole: participants were slower in initiating a movement when a cue was presented compared to when no cue was presented, indicating that participants integrated the prospects of pain from the instrumental responses as well as that engendered by the cues, possibly resulting in a summation.

Second, task characteristics may have contributed to the pattern of responding found in the group as a whole, as was also observed in the reward-seeking and equally important-group. Our experiment fundamentally differs from classic PIT (avoidance) experiments in humans on which we based our hypotheses (e.g., Lewis et al., 2013; Nadler et al., 2011; Watson, Wiers, Hommel, & De Wit, 2014). To the best of our knowledge, our study is the first one to explore the effects of Pavlovian cues in a context where the negative outcome—in our case, pain—can both be actively approached as well as actively avoided. Studies investigating PIT-effects in avoidance, have mostly used designs in which participants had two available response options, both of which resulted in averting/preventing a different negative event (e.g., Lewis et al., 2013; Nadler et al., 2011). Furthermore, the negative outcomes were reinforcers specific to the task at hand, rather than primary or secondary reinforcers as used here. Our study more closely resembles the study of Van Meurs et al. (2014), who studied the generalization of (maladaptive) avoidance behavior. These authors gave participants two response options: either an 'avoidant' response which resulted in the avoidance of painful stimulation but also in the loss of crops (relevant for the task) or harvesting crops, which resulted in the administration of a painful stimulus. As such, both response options had a negative and a positive consequence, which may be considered a double approach-avoidance (conflict) situation (Lewin, 1935; Miller, 1944). In our study, this trade-off between positive and negative consequences was present as well, but may have not been as strong. More specifically, we had a trade-off between the chance of receiving pain and the effort required to perform the movement: the higher the chance of pain—related to the goal to avoid pain—the less effort was needed to perform the movement—related to the (instructed) goal to complete the movements as fast as possible—, and vice versa. However, if participants exerted more effort, safe movements could be performed as fast as painful movements, which may have created an imbalance in the trade-off, which in turn may have affected participants' choices. Future studies should increase the difficulty of movement, or stress accuracy of movement instead of speed of movement to overcome this limitation.

Third, and related to the previous point, the pattern of responding observed in our study may reflect an influence of Pavlovian cues on instrumental behavior, although in a different way than we expected. It is possible to interpret the three movement pathways (Responses, R) in our experiment as follows: initially, the first movement path (R1) is associated with a painful outcome (O-). The same is true for the second (middle) pathway (R2), albeit using a different reinforcement rate. The third movement path (R3) however is associated with safety, which from a functional perspective can be viewed as a positive outcome (O+). As such, participants learned 3 associations in the instrumental phase: R1-O-, R2-O-, and R3-O+. In the Pavlovian phase, participants then learned an association between the first cue (S1) and a painful outcome (O-), a second cue (S2) and a new, positive outcome (O+), and lastly a third cue (S3) with neither outcome, which may have been interpreted as safety as well (O+). Thus, the following associations were learned: S1-O-, S2-O+, and S3-O+. Our results seem to suggest that the CS functions as a 'reminder' cue to select a certain action (in our case avoidance behavior), by virtue of the shared outcome. This reminder function may be particularly the case for S1 (facilitates R1 via O-) and S3 (facilitates R3 via O+), irrespective of the value of the outcome. Our results are in line with the finding in appetitive PIT that cues bias responding toward a certain response option, regardless of (the desirability of) the outcome. In the context of food for example, Watson et al. (2014) found elevated responses toward food outcomes, although participants were satiated. Similar effects have been observed in smoking (Hogarth, 2012; Hogarth & Chase, 2011). We may posit that our research demonstrates that cues bias responding toward a specific action, even if the outcome of that action is undesirable, at least in an experimental context. However, such claims cannot be made based on this study alone, and more research is warranted to see whether this hypothesis holds true. At the least, if we frame our experiment as outlined above, we demonstrated that in this experiment, participants responded congruently based on the outcome presented. However, this behavior may have been caused by social desirability, and as such, caution is needed when interpreting the results. To assess the impact of similarities in valence, future studies could introduce other painful stimuli of an equal valence, or add another stimulus modality (e.g., heat stimulation) and pain threshold stimuli.

Fourth, another viable explanation for our results stems from an expectancy-based framework (cf. Dickinson & Balleine, 1994). It may very well be that the presentation of a pain cue elicits the expectation of pain, and as a consequence, participants may have reasoned along the lines of "I am receiving pain anyway, so I might as well do the movement that is the fastest/easiest". The fact that our test phase did not take place under extinction may have allowed participants to confirm this (false) belief. We therefore recommend including at the least nominal extinction in the test phase. On the other hand, it may also be that the participants' behavior reflects the 'confrontational' approach as mentioned in the fear-avoidance model: participants confront themselves with the painful movements.

Lastly, it is possible that differences in exposure to the outcomes and CSs may have contributed to differences in pain intensity experiences—that is, increased pain sensitivity in the case of sensitization or decreased pain sensitivity in the case of habituation—or differences in beliefs about the contingencies. Future studies might include measurements of pain intensity and pain expectancy after each block to control for such effects. To conclude, our study has shown that Pavlovian cues may influence behavioral choices, in the sense that they seem to prioritize actions that shared a similar outcome with these cues, even when these outcomes are undesirable. Further research that elucidates the underlying mechanisms is warranted.

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Figure Captions

Figure 1. Overview of the experimental environment. Movement is allowed along the x-, y-, and z-axis, as indicated by the white surface. White arrows indicate the Haptically defined movement positions. The green arrows indicate the visual distance on screen. The yellow arrows indicate. the maximal movement distance. A red cube of 3.5 cm x 3.5 cm at the bottom of the screen indicates the start position. The three red gates in the middle represent the three possible movement paths: the left gate is associated with a 80% chance of receiving a painful stimulus; the middle gate is associated with a 50% chance of receiving a painful stimulus; the right gate is associated with safety. A red gate at the top left of the screen indicates the end of a movement. Counter bars indicate the number of movements (to be) made.

Figure 2. Movement examples. Examples of movements performed by a participant for the left, middle, and right path respectively.

Figure 3. Mean Maximum distance during the test phase.

Table 1

Mean and standard devation for response latency and response duration in milliseconds per block and per CS type

Variable	CS type	Block			
		1	2	3	4
		M(SD)	*M(SD)*	*M(SD)*	*M(SD)*
Response latency	None	472(187)	434(121)	415(128)	412(126)
	Pain	598(371)	438(131)	447(155)	408(111)
	Reward	555(369)	426(129)	423(121)	403(102)
	Neutral	597(354)	453(151)	427(133)	426(115)
Response duration	None	2655(936)	2446(932)	2335(701)	2328(736)
	Pain	2601(861)	2373(739)	2290(664)	2453(1302)
	Reward	2777(786)	2624(659)	2436(677)	2255(555)
	Neutral	2817(933)	2585(900)	2456(643)	2309(587)

Fig. 1

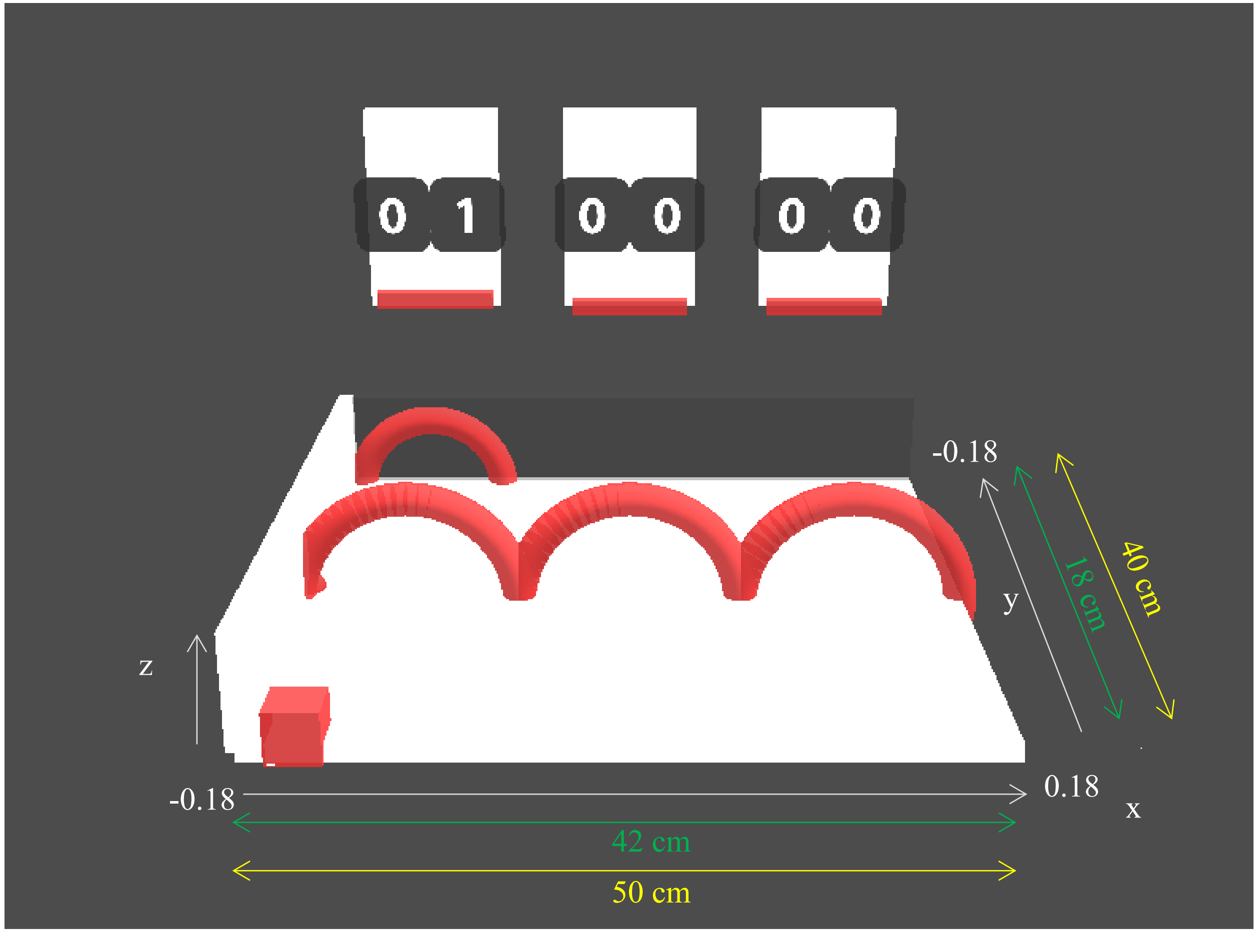


Fig.2

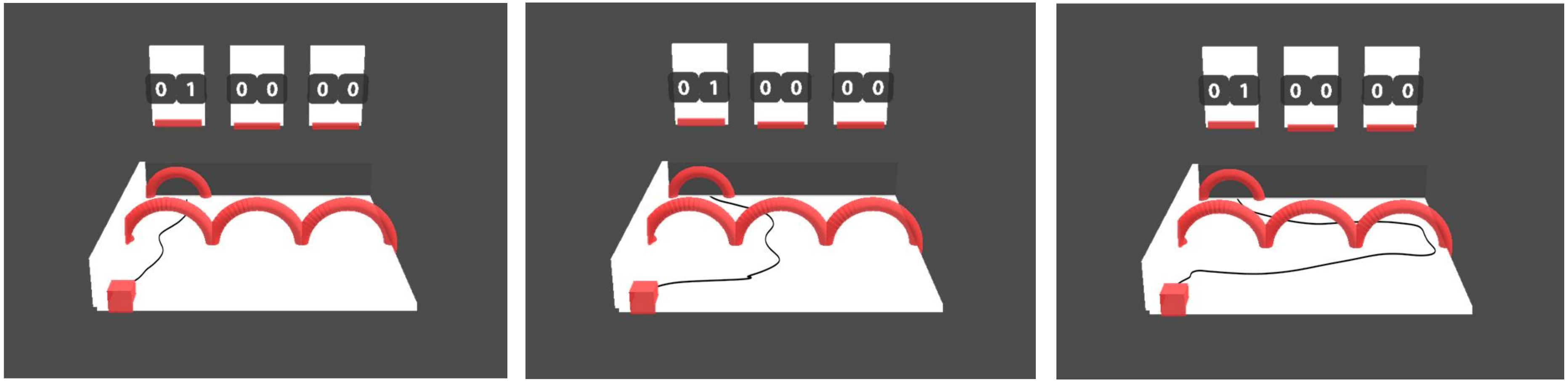
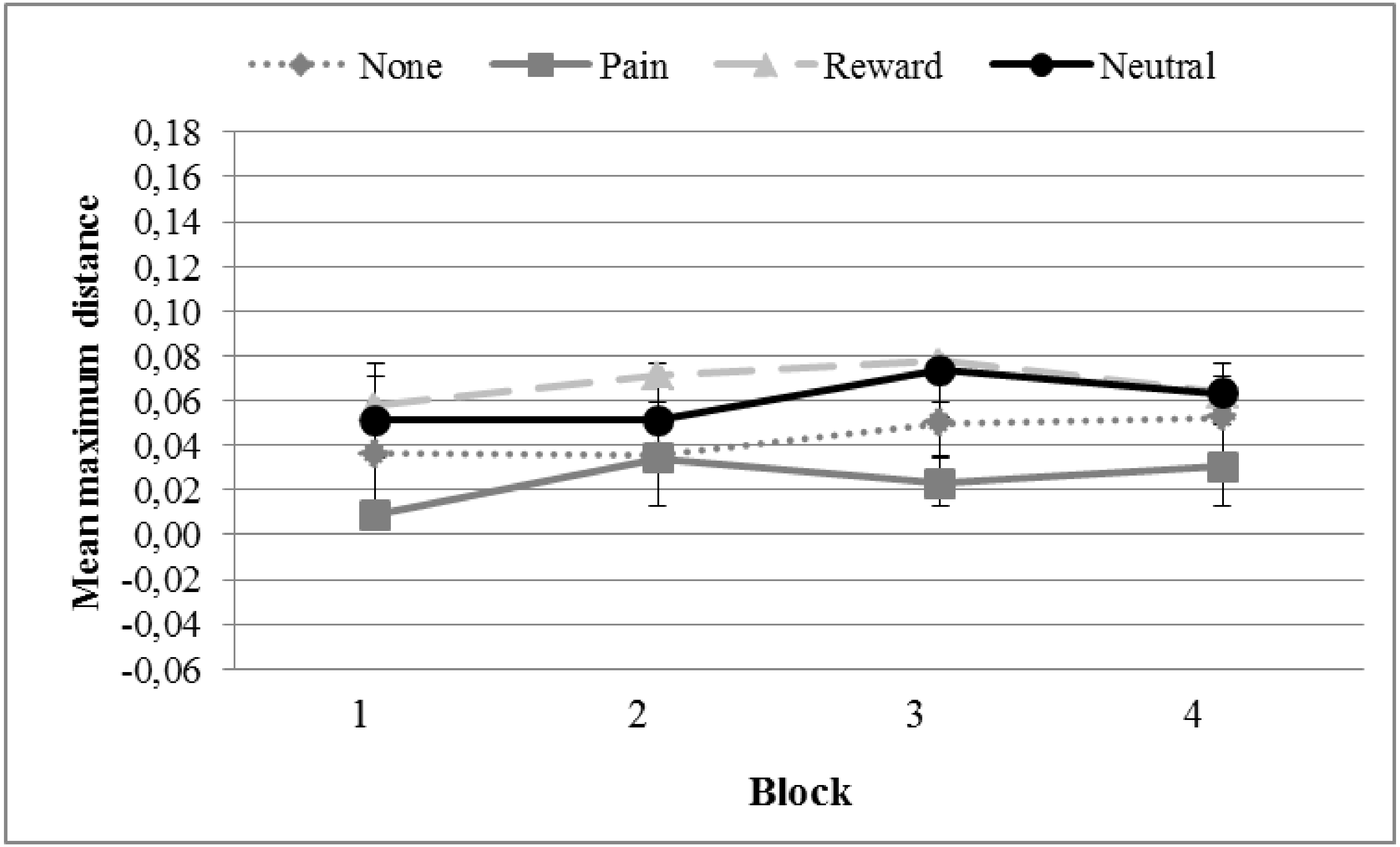


Fig. 3


None
Pain
Reward
Neutral
Mean maximum distance
0,18
0,16
0,14
0,12
0,10
0,08
0,06
0,04
0,02
0,00
-0,02
-0,04
-0,06
1
2
3
4
Block